# General

## Guideline Title

Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines.

## Bibliographic Source(s)

Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S. [228 references] PubMed

## Guideline Status

This is the current release of the guideline.

# Recommendations

## Major Recommendations

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

<u>Diagnosis of Suspected First Lower Extremity Deep Vein Thrombosis (DVT)</u>

Alternatives to Venography for the Evaluation of Suspected First Lower Extremity DVT

In patients with a suspected first lower extremity DVT, the expert panel suggests that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B).

Note: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

Testing Using Risk Stratification

In patients with a low pretest probability of first lower extremity DVT (see Fig. 1 in the original guideline document), the expert panel recommends one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer, or (iii) compression ultrasonography (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons), (ii) venography (Grade 1B for all comparisons), or (iii) whole-leg ultrasound (US) (Grade 2B for all comparisons). The expert panel suggests initial use of a moderately sensitive (Grade 2C) or highly sensitive (Grade 2B) D-dimer rather than proximal CUS.

*Remarks*: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (e.g., when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, the expert panel suggests computed tomography (CT) scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative (see Fig. 1 in the original guideline document), the expert panel recommends no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons). If the proximal CUS is negative, the expert panel recommends no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons).

If the D-dimer is positive (see Fig. 1 in the original guideline document), the expert panel suggests further testing with CUS of the proximal veins rather than (i) whole-leg ultrasonography (US) (Grade 2C) or (ii) venography (Grade 1B). If CUS of the proximal veins is positive, the expert panel suggests treating for DVT and performing no further testing over performing confirmatory venography (Grade 2C).

*Remarks*: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (e.g., a short segment of venous noncompressibility).

In patients with a moderate pretest probability of first lower extremity DVT (see Fig. 2 in the original guideline document), the expert panel recommends one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than (i) no testing (Grade 1B for all comparisons) or (ii) venography (Grade 1B for all comparisons). The expert panel suggests initial use of a highly sensitive D-dimer rather than US (Grade 2C).

*Remarks*: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (e.g., when leg casting or excessive subcutaneous [SC] tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, the expert panel suggests computed tomography (CT) scan venography, magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative (see Fig. 2 in the original guideline document), the expert panel recommends no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons).

If the highly sensitive D-dimer is positive, the expert panel recommends proximal CUS or whole-leg US rather than no testing (Grade 1B for all comparisons) or venography (Grade 1B for all comparisons).

If proximal CUS is chosen as the initial test and is negative (see Fig. 2 in the original guideline document), the expert panel recommends (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) or venography (Grade 2B). In patients with a negative proximal CUS but a positive D-dimer, the expert panel recommends repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B).

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, the expert panel recommends no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons).

If whole-leg US is negative (see Fig. 2 in the original guideline document), the expert panel recommends no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons). If proximal CUS is positive, the expert panel recommends treating for DVT rather than confirmatory venography (Grade 1B). If isolated distal DVT is detected on whole-leg US, the expert panel suggests serial testing to rule out proximal extension over treatment (Grade 2C).

*Remarks*: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in the National Guideline Clearinghouse (NGC) summary of the American College of Chest Physicians (ACCP) guideline Antithrombotic therapy for VTE disease are more likely to benefit from treatment over repeat US.

In patients with a high pretest probability of first lower extremity DVT (see Fig. 3 in the original guideline document), the expert panel recommends either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) or venography (Grade 1B for all comparisons).

*Remarks*: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and D-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (e.g., when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, the expert panel suggests CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT (see Fig. 3 in the original guideline document), the expert panel recommends treatment rather than confirmatory venography (Grade 1B).

In patients with a negative proximal CUS (see Fig. 3 in the original guideline document), the expert panel recommends additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) or venography (Grade 2B for all comparisons). The expert panel recommends that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B). In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, the expert panel recommends no further testing over venography or additional US (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US).

The expert panel recommends that in patients with high pretest probability (see Fig. 3 in the original guideline document), moderately or highly sensitive D-dimer assays should not be used as stand-alone tests to rule out DVT (Grade 1B).

If risk stratification is not performed in patients with suspected first lower extremity DVT (see Fig. 4 in the original guideline document), the expert panel recommends one of the following initial tests: (i) proximal CUS or (ii) whole-leg US, rather than (i) no testing (Grade 1B), (ii) venography (Grade 1B), or D-dimer testing (Grade 2B).

*Remarks*: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (e.g., when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, the expert panel suggests that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

The expert panel recommends that patients with a negative proximal CUS (see Fig. 4 in the original guideline document) undergo testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B). In patients with a negative proximal CUS, the expert panel suggests D-dimer rather than routine serial CUS (Grade 2B) or whole-leg US (Grade 2C). The expert panel recommends that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing (Grade 1B for both comparisons).

The expert panel recommends that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US (see Figs. 4 and 5 in the original guideline document), no further testing be performed rather than venography (Grade 1B).

If proximal US is positive for DVT (see Fig. 4 in the original guideline document), the expert panel recommends treatment rather than confirmatory venography (Grade 1B). If isolated distal DVT is detected on whole-leg US (see Fig. 5 in the original guideline document), the expert panel suggests serial testing to rule out proximal extension over treatment (Grade 2C).

*Remarks*: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in the NGC summary of the ACCP guideline Antithrombotic therapy for VTE disease are more likely to benefit from treatment over repeat US.

In patients with suspected first lower extremity DVT, the expert panel recommends against the routine use of CT venography or magnetic resonance imaging (MRI) (Grade 1C).

Diagnosis of Suspected Recurrent Lower Extremity DVT

In patients suspected of having recurrent lower extremity DVT (see Fig. 6 in the original guideline document), the expert panel recommends initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B).

*Remarks*: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive (see Fig. 7 in the original guideline document), the expert panel recommends proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons).

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of <2 mm), the expert panel suggests at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B).

*Remarks*: In patients with an abnormal proximal US at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of <2 mm).

The expert panel recommends that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS (see Figs. 6 and 7 in the original guideline document) undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B).

If CUS of the proximal veins is positive (see Figs. 6 and 7 in the original guideline document), the expert panel recommends treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a ≥4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result).

*Remarks*: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over treatment (in the case of ≥4-mm increase in venous diameter).

In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (e.g., an increase in residual venous diameter of <4 but ≥2 mm) (see Fig. 8 in the original guideline document), the expert panel recommends further testing with venography, if available (Grade 1B); serial proximal CUS (Grade 2B) or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive (Grade 2B), as opposed to other testing strategies or treatment.

In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison (see Fig. 9 in the original guideline document), the expert panel recommends further testing with venography, if available (Grade 1B) or a highly sensitive D-dimer (Grade 2B) over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, the expert panel suggests no further testing over venography (Grade 2C). In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, the expert panel suggests venography if available over empirical treatment of recurrence (Grade 2C).

*Remarks*: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

Diagnosis of Pregnancy-Related DVT

In pregnant patients suspected of having lower extremity DVT (see Fig. 10 in the original guideline document), the expert panel recommends initial evaluation with proximal CUS over other initial tests, including a whole-leg US (Grade 2C), moderately sensitive D-dimer (Grade 2C), highly sensitive D-dimer (Grade 1B), or venography (Grade 1B).

In pregnant patients with suspected DVT in whom initial proximal CUS is negative, the expert panel suggests further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) or a sensitive D-dimer done at the time of presentation (Grade 2B) over no further testing for DVT. The expert panel recommends that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT (Grade 1B) and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7) rather than venography (Grade 1B) or whole-leg US (Grade 2C).

In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS (see Fig. 11 in the original guideline document), the expert panel suggests further testing with either Doppler US of the iliac vein (Grade 2C), venography (Grade 2C), or direct MRI (Grade 2C), rather than standard serial CUS of the proximal deep veins.

Diagnosis of Upper Extremity DVT

In patients suspected of having upper extremity DVT (see Fig. 12 in the original guideline document), the expert panel suggests initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C).

In patients with suspected upper extremity DVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT (see Fig. 12 in the original guideline document), the expert panel suggests further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C).

In patients with suspected upper extremity DVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, the expert panel recommends no further testing, rather than confirmatory venography (Grade 1C). The expert panel suggests that patients with an initial combined-modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms (Grade 2B), in which case testing to evaluate for the presence an alternative diagnosis should be performed. The expert panel suggests that patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography (Grade 2C).

*Remarks*: Further radiologic testing (serial US or venographic-based imaging or CT scan/MR to seek an alternative diagnosis) rather than d-dimer testing is preferable in patients with comorbid conditions typically associated with elevated D-dimer levels.

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

| Study Design | Quality of Evidence | Lower if | Higher if |
|---|---|---|---|
| Randomized Trial → | High | Risk of bias<br>-1 Serious<br>-2 Very serious | Large effect<br>+1 Large<br>+2 Very large |
| | Moderate | | |
| | | Inconsistency<br>-1 Serious<br>-2 Very serious | Dose response<br>+1 Evidence of a gradient |
| Observational Study → | Low | | |
| | Very Low | Indirectness<br>-1 Serious<br>-2 Very serious | All plausible confounding<br>+1 Would produce a demonstrated effect or<br>+1 Would suggest a spurious effect when result show no effect |
| | | Imprecision<br>-1 Serious<br>-2 Very serious | |
| | | Publication bias<br>-1 Likely<br>-2 Very likely | |

Strength of the Recommendations Grading System

| Grade of Recommendation* | Benefit vs. Risk and Burdens | Methodologic Quality of Supporting Evidence | Implications |
|---|---|---|---|
| Strong recommendation, high-quality evidence, Grade 1A | Benefits clearly outweigh risk and burdens or vice versa | Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies | Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect |
| Strong | Benefits clearly outweigh | Evidence from RCTs with important | Recommendation can apply to most patients in |

| Grade of Recommendation* | Benefit vs. Risk and Burdens | Methodologic Quality of Supporting Evidence | Implications |
|---|---|---|---|
| Strong recommendation, moderate-quality evidence, Grade 1B | Benefits clearly outweigh risk and burdens or vice versa | limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies | most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate |
| Strong recommendation, low- or very-low-quality evidence, Grade 1C | Benefits clearly outweigh risk and burdens or vice versa | Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence | Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate |
| Weak recommendation, high-quality evidence, Grade 2A | Benefits closely balanced with risks and burden | Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies | The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect |
| Weak recommendation, moderate-quality evidence, Grade 2B | Benefits closely balanced with risks and burden | Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies | Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate |
| Weak recommendation, low- or very-low-quality evidence, Grade 2C | Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced | Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence | Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate |

*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.

## Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Figure 1: Recommendations for evaluation of suspected first lower DVT: patients with low pretest probability (PTP) for DVT
- Figure 2: Recommendations for evaluation of suspected first lower extremity DVT: patients with moderate pretest probability (PTP) for DVT
- Figure 3: Recommendations for evaluation of suspected first lower extremity DVT: patients with high pretest probability (PTP) for DVT
- Figure 4: Recommendations for evaluation of suspected first lower extremity DVT: risk stratification not performed
- Figure 5: Use of whole-leg US
- Figure 6: Recommendations for evaluation of suspected lower extremity recurrent DVT: proximal US as initial test
- Figure 7: Recommendations for evaluation of suspected lower extremity recurrent DVT: highly sensitive D-dimer as initial test
- Figure 8: Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following nondiagnostic proximal US and prior US result available for comparison
- Figure 9: Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following non-diagnostic proximal US and prior US result not available for comparison
- Figure 10: Recommendations for evaluation of suspected pregnancy-related lower extremity DVT
- Figure 11: Recommendations for evaluation of suspected pregnancy-related lower extremity DVT: suspected isolated iliac vein DVT
- Figure 12: Recommendations for evaluation of suspected upper extremity DVT
- Figure 13: Use of venography

# Scope

## Disease/Condition(s)

Deep vein thrombosis (DVT), including first DVT, recurrent DVT, upper extremity DVT, and DVT during pregnancy

## Guideline Category

Diagnosis

Evaluation

Prevention

Risk Assessment

Treatment

## Clinical Specialty

Cardiology

Critical Care

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Nursing

Obstetrics and Gynecology

Oncology

Orthopedic Surgery

Pulmonary Medicine

Radiology

Surgery

Thoracic Surgery

## Intended Users

Advanced Practice Nurses

Health Care Providers

Hospitals

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

- To update evidence-based recommendations for the use of anticoagulant therapy for the management of thromboembolic conditions
- To offer guidance for many common anticoagulation-related management problems
- To optimize patient-important health outcomes and the processes of care for patients who have experienced or are at risk for thrombotic events
- To identify optimal strategies for the diagnosis of deep vein thrombosis (DVT) in ambulatory adults

## Target Population

Ambulatory adult patients at risk for deep vein thrombosis (DVT), including pregnant women

## Interventions and Practices Considered

1. Clinical assessment of pretest probability of deep vein thrombosis (DVT)
2. D-dimer testing (moderately sensitive or highly sensitive)
3. Compression ultrasonography (CUS) of the proximal veins
4. Venography
5. Whole-leg ultrasound
6. Doppler ultrasound of the iliac vein
7. Magnetic resonance imaging
8. Considerations for pregnancy-related DVT and upper extremity DVT

## Major Outcomes Considered

- Accuracy (sensitivity and specificity of diagnostic tests)
- Incidence of false-positive and false-negative results
- Fatal and nonfatal pulmonary embolism (PE)
- Fatal bleeding
- Nonfatal intracranial bleeding
- Major, nonfatal, non-intracranial bleeding

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Defining the Clinical Questions—Population, Intervention, Comparator, and Outcome

The thrombosis expert on the Executive Committee along with the deputy editors took primary responsibility for defining the scope of the clinical questions that each article would address. For each question, the topic editor and deputy editor defined the relevant population, alternative

management strategies (intervention and comparator), and the outcomes (i.e., population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework for formulating study inclusion and exclusion criteria and guided the search for relevant evidence (systematic reviews and original studies). Panels typically restricted included studies to randomized controlled trials (RCTs) for intervention questions but included observational studies when there was a paucity of RCT data addressing an intervention and for questions of risk assessment. Readers can find these PICO questions in the first table of each article. One or more recommendations could be formulated for each clinical question.

Identifying the Evidence

To identify the relevant evidence, a team of methodologists and medical librarians at the Oregon Health & Science University Evidence-based Practice Center conducted literature searches of Medline, the Cochrane Library, and the Database of Abstracts of Reviews of Effects. For each article, the team conducted a search for systematic reviews and another for original studies encompassing the main populations and interventions for that article. These searches included studies indexed from week 1, January 2005, forward because Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) searches were carried out up to that date (search strategies are available on request). Many articles supplemented these searches with more-focused searches addressing specific clinical questions. When clinical questions had not been covered in AT8, searches commenced at a date relevant to each intervention.

Titles and abstracts retrieved from bibliographic database searches generally were screened in duplicate, and full-text articles were retrieved for further review. Consensus on whether individual studies fulfilled inclusion criteria was achieved for each study between two reviewers. If consensus could not be achieved, the topic editor and other topic panelists were brought into the discussion. Deputy editors reviewed lists of included studies from the database searches in order to identify any potentially missed studies. Additional studies identified were then retrieved for further evaluation.

Topic panels also searched the same bibliographic databases for systematic reviews addressing each PICO question. The quality of reviews was assessed using principles embodied in prior instruments addressing methodologic quality of systematic reviews, and wherever possible, current high-quality systematic reviews were used as the source of summary estimates. Reviews were also used to identify additional studies to complement the database searches.

# Number of Source Documents

Not stated

# Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

# Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

| Study Design | Quality of Evidence | Lower if | Higher if |
|---|---|---|---|
| Randomized Trial → | High | Risk of bias<br>-1 Serious<br>-2 Very serious | Large effect<br>+1 Large<br>+2 Very large |
| | Moderate | | |
| Observational Study → | Low | Inconsistency<br>-1 Serious<br>-2 Very serious | Dose response<br>+1 Evidence of a gradient |
| | Very Low | Indirectness<br>-1 Serious<br>-2 Very serious | All plausible confounding<br>+1 Would produce a demonstrated effect or<br><br>+1 Would suggest a spurious effect when result show no effect |
| | | Imprecision | |

| Study Design | Quality of Evidence | Lower if 1 Serious -2 Very serious | Higher if |
|---|---|---|---|
| | | Publication bias -1 Likely -2 Very likely | |

# Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

# Description of the Methods Used to Analyze the Evidence

General Methods

Assessing Studies and Summarizing Evidence

*Evaluating Risk of Bias in Individual Studies*

The expert panel developed and applied uniform criteria for evaluating the risk of bias associated with individual randomized controlled trials (RCTs) based on the criteria recommended by the Cochrane Collaboration (Table 1 in the methodology companion [see the "Availability of Companion Documents" field]). Although all authors assessed risk of bias for individual studies, because of resource limitations, the panel summarized the results of the risk of bias for only a minority of the recommendations. Readers can find these assessments in the online data supplements. For most recommendations for which such tables were not developed, Evidence Profiles that typically provide information on the risk of bias in footnotes were developed.

The panel also developed specific criteria for assessing the risk of bias of observational studies (cohort studies with concurrent controls, cohort studies with historical controls, case-control studies, or case series). Again, these were based on the evidence-based domains recommended by the Cochrane Collaboration for observational studies.

Studies without internal comparisons were termed "cohort studies without internal controls" if they met the following criteria:

1. A protocol existed before the date of commencement of data collection.
2. A definition of inclusion and exclusion criteria was available.
3. The study reported the number of excluded patients.
4. The study conducted a standardized follow-up, including description of all of the following: schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes.
5. The study reported all losses to follow-up.

The panel labeled studies that did not meet these criteria as "case series." No distinction was made between prospective and retrospective studies because although prospective studies may on average be of higher quality, individual prospective studies may have a significant risk of bias and specific retrospective studies may not. For questions related to risk assessment, the panel evaluated the risk of bias of individual studies using the following criteria: valid outcome assessment, including blinding when appropriate; adjustment for between-group differences; and minimal loss to follow-up.

*Evaluating Quality of Bodies of Evidence*

The expert panel assessed evidence across studies on an outcome-by-outcome basis using criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. The expert panel defined quality of evidence as their confidence in the estimate of the effect to support a recommendation. RCTs start as high-quality evidence and observational studies as low-quality evidence. Additional factors that affect this rating of quality include the risk of bias; precision, consistency, and directness of results; likelihood of publication bias; and presence of very large effects. The American College of Chest Physicians (ACCP) adaptation of the GRADE system differs only in that the quality of a body of evidence can be high (A), moderate (B), or low (C); GRADE also provides a category for very-low-quality evidence. See

the "Rating Scheme for the Strength of the Evidence" field.

Often, the panel found that the quality of the evidence differed across outcomes. For example, in assessing the quality of evidence for thienopyridines vs warfarin in patients undergoing percutaneous coronary interventions, the panel determined the evidence to be of moderate quality for mortality, nonfatal myocardial infarction, and revascularization but of low quality for major bleeding.

The panel then made a rating of the quality of the entire body of evidence bearing on the effect of alternative management strategies for each clinical question. In other words, the panel assessed the quality across outcomes, including both benefits and harms. Quality for each recommendation was the lowest quality rating of the outcomes judged as critical (as opposed to important, but not critical).

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, venous thromboembolism [VTE], myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. The evidence summaries (Evidence Profiles and Summary of Findings tables), therefore, include a presentation of relative effects (where possible as relative risks because they are easier to understand than odds ratios [ORs]) of intervention vs control management strategies.

Trading off desirable and undesirable consequences (e.g., thrombosis vs bleeding) requires, however, estimates of absolute effect. For example, in patients with atrial fibrillation, warfarin results in a 66% relative risk reduction in nonfatal stroke. This comes at a cost of inconvenience, lifestyle restrictions, and risk of bleeding. For patients with a CHADS (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke) score of ≥3, the 66% relative risk reduction translates into an absolute reduction of 6.3% (63 in 1,000) per year. Virtually all patients will consider this worthwhile. On the other hand, for patients with a CHADS score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients may consider this reduction not worth the undesirable consequences of warfarin use.

The panel calculated absolute effects by applying relative risks to estimates of control group risk. For instance, if control group risk of thrombosis is 4% and relative risk with an intervention is 50%, then the absolute difference between intervention and control is 4% of 50% or 2%, and the number needed to treat to prevent an episode of thrombosis is 100/2 or 50. In many cases, the Summary of Findings tables present effects as events prevented (or caused) per 1,000 patients. In this hypothetical example, the effect would be 20 events per 1,000 patients.

Whenever valid prognostic data were available from observational studies, they were used to estimate control group risks. When credible results from observational and prognostic studies were not available, risk estimates from control groups of RCTs were used.

*Considering Subgroup-Specific Relative and Absolute Effects*

Whenever the expert panel identified credible evidence that the relative effects vary across distinguishable subgroups of patients (i.e., interaction between the intervention and a patient characteristic), the respective relative effects were considered separately. The panel then calculated the associated absolute effects.

Even when the relative effect is the same, the absolute magnitude of treatment effects may differ in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for patients with atrial fibrillation is likely close to 50% across risk groups, this translates into an absolute risk reduction of <1% per year in the lowest-risk groups and ~5% per year in the highest-risk groups.

The expert panel included control group risks and absolute-effect estimates for different groups in the summaries of effect when (and only when) two conditions were present. First, they required validated prognostic models or, at the very least, credible strategies for clinicians to easily identify higher- and lower-risk patients. Second, the panel identified varying risk groups only when recommendations differed in strength or direction between groups. Both conditions were met, for instance, in the atrial fibrillation recommendations in which strong recommendations in favor of anticoagulation were restricted to the higher-risk patients.

*Conducting Meta-analyses*

When pooled estimates of effects were not available from existing high-quality systematic reviews, the panel performed meta-analyses if the data were sufficiently homogeneous. When pooling two studies, they used a fixed-effects model. When three or more studies were available for generating a pooled estimate, they used a random-effects model as the primary analysis and a fixed-effects model as a secondary analysis. If there were discrepancies between the two, the panel considered the following reasons: If there was substantial heterogeneity leading to wider confidence intervals (CIs) with the random-effects model, the panel considered that model more trustworthy, and if the discrepancy was due to a single large dominant study with a result substantially different from smaller studies, they considered the fixed-effects model more trustworthy. The panel also assessed statistical heterogeneity using both a $\chi^2$ test and $I^2$ as well as assessed possible explanations of heterogeneity considering a priori-generated hypotheses.

*Summary Tables*

When resources permitted, the expert panel used a standardized approach for summarizing the evidence and methodology of individual studies. These summaries appear in the online data supplements. Wherever possible, the expert panel reported nonfatal events (e.g., nonfatal stroke) so that there is no overlap with the number of fatal events reported.

For a large number of recommendations, the expert panel summarized the quality of the body of evidence (see the "Rating Scheme for the Strength of the Evidence" field) and estimates of relative and absolute effect of alternative management strategies using the methods of the GRADE Working Group. Evidence Profiles summarize the quality of the body of evidence and when evidence comes from randomized trials, generally include a presentation of reviewer assessment of risk of bias, precision, consistency, directness, and publication bias associated with each outcome. As specified in GRADE methodology, the overall quality of evidence represents the lowest quality of any critical outcome.

Evidence Profiles can be found in the online data supplement. The format for these tables was determined through a formal survey of panelists that evaluated the panelists' preferences for alternative presentations and the impact of these presentations on their understanding of the evidence. The text in the printed version of Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) recommendations includes more succinct Summary of Findings tables, which include the overall quality assessment as well as the relative and absolute effect sizes for each outcome. Use of an associated computer program facilitated the production of the Evidence Profiles and Summary of Findings tables which are listed in the original guideline document.

<u>Specific Methods for This Guideline</u>

Eligible studies included both those addressing diagnostic accuracy (cross-sectional accuracy studies) and studies that assessed clinical outcomes such as deep vein thrombosis (DVT) or pulmonary embolism (PE) during follow-up (prospective cohort management studies and randomized controlled trials [RCTs]). In typical management studies, investigators follow untreated patients with negative test results and record the proportion of patients who develop venous thromboembolism (VTE). For each section, the panel developed corresponding methodology tables that included information on the study question (in terms of population, intervention, comparator, and outcome), the type of evidence assessed (meta-analysis or original study; cross-sectional study or management cohort or randomized trial), and selected details of study execution (inclusion of consecutive patients and independence of test result assessment). Findings of individual studies and meta-analyses are presented in descriptive tables and, when feasible, overall findings relating to each question are summarized as Evidence Profiles and Summary of Findings tables.

For accuracy studies, the panel extracted sensitivity and specificity and then estimated the effect on patient-important outcomes (e.g., DVT, PE, death, bleeding in treated patients) that would be associated with this level of accuracy, assuming prevalences of DVT that correspond to high, moderate, and low pretest probability categories. For studies in which the diagnostic test was used to manage patients (i.e., management studies), the incidence of VTE during follow-up was determined for patients in whom anticoagulation and additional diagnostic testing were withheld on the basis of negative test results.

Following the approach articulated by GRADE for formulation of recommendations related to diagnosis, the panel first considered the quality of evidence (representing the confidence that the testing strategy would result in patient outcomes that support a particular recommendation). The panel initially considered studies as providing high quality of evidence, unless rated down because of the following factors: risk of bias (e.g., unrepresentative patients, lack of independent assessment of test and criterion standard), inconsistency (differences among study results), indirectness (with respect to the population studied, the tests performed, or the outcome measured), lack of precision, and risk of publication bias. Unless otherwise explicitly stated, the quality of evidence obtained from cross-sectional accuracy studies was lowered by one level because of the indirectness with which sensitivity and specificity corresponds to patient-important outcomes.

Typically, diagnostic strategies for DVT have been deemed acceptable if they have demonstrated no more than a 2% frequency of VTE during follow-up (a rate comparable to that seen when DVT is excluded by venography) in management studies in which treatment is withheld on the basis of a negative result. Management studies that assess the follow-up frequency of VTE after negative diagnostic testing provide no information regarding false-positive diagnoses for DVT. Patients who are misdiagnosed with DVT will be prescribed unnecessary anticoagulants and some will suffer major bleeding as a result. To overcome this limitation, we estimated the risk of major bleeding associated with different diagnostic strategies. These estimates were based on (1) the proportion of patients diagnosed with DVT (derived from sensitivity and specificity, with the assumption that all diagnosed DVT are treated), and (2) the frequency of major bleeding with 3 months of therapeutic-dose anticoagulants in cohort studies and randomized trials of patients with VTE. Because the evidence regarding major bleeding emerging from these models is indirect, it is generally rated as no higher than moderate quality.

Refer to the original guideline document for additional specific methodology information.


# Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

# Description of Methods Used to Formulate the Recommendations

Composition and Selection of Topic Panel Members

The American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee selected panel members for each article. A topic editor and a deputy editor led each of the AT9 panels issuing recommendations. The topic editor was the person primarily responsible for each article and was required to be a methodologist without serious financial or intellectual conflict of interest for any of the article's recommendations. In all but one case, the topic editor also was a clinician. The Executive Committee chose these individuals on the basis of their previous experience with guideline development and, in particular, their familiarity with methods developed by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. These topic editors and all panel members were approved by the ACCP Health and Science Policy (HSP) Committee after review of their conflict of interest disclosures.

Criteria for selection of the remainder of the panel members, including the deputy editor-thrombosis expert, were an established record in the relevant clinical or research area, international and gender representation, and an absence of financial conflicts of interest that were judged unacceptable. Some of the panelists had prior experience on ACCP guidelines in this area and represented the thrombosis community, but there was substantial turnover from the previous edition. After an international request for applications broadcast through multiple medical societies, the Executive Committee nominated individual topic editors and deputy editors and collaborated with them to identify and nominate other topic panel members.

The ACCP HSP Committee reviewed all nominees and approved all panel members after review of their curricula vitae and conflict of interest disclosures. Of 150 nominees, 137 were approved, 18 were approved with management of conflicts of interest (i.e., regular disclosures and review of ongoing conflicts as the process progressed), and 13 were disapproved as a result of the magnitude of financial conflicts of interest. Articles associated with recommendations included from seven to 14 panel members. Patients or representatives of specific stakeholder groups were not included on topic panels.

Each topic panel also included a frontline physician working in the relevant area who was neither an expert in thrombosis nor a methodologist or clinical investigator. These individuals were chosen in consultation with the topic editors and the ACCP HSP Committee. These clinicians were charged with the following: (1) proposing important real-world clinical questions on the prevention, diagnosis, and treatment of thrombosis that were not addressed in Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) and (2) reviewing the draft manuscripts and recommendations to assess the usability of the guidelines and the feasibility of implementation of AT9 recommendations.

To address issues of economic efficiency six health economist-physicians were included on the AT9 topic panels charged with making recommendations. These resource consultants were selected and approved through identical procedures to those for topic editors and panel members.

Ensuring Consistency Across Articles

A number of strategies were used to ensure consistency across articles, and one panel member participated extensively in the formulation of clinical questions for each article. To ensure consistency of judgments regarding bleeding, another panel member was responsible for standardizing the approach to bleeding outcomes and participated in multiple topic panels. Additionally, to ensure consistency in the trade-offs between thrombotic and bleeding events, all articles used the same ratings of values and preferences (described in more detail in the methodology companion [see the "Availability of Companion Documents" field]). Because some of the same evidence summaries were relevant to several articles, five individuals were chosen to participate in each of the articles addressing coronary artery disease, stroke, and peripheral arterial disease.

In AT9, prevention of venous thromboembolism (VTE) is addressed in three articles as opposed to a single article as was done in AT8. The prevention topic editors and deputy editors and those of the stroke article (which includes thromboprophylaxis recommendations) participated in multiple conference calls to develop and harmonize the approach to prevention and to ensure consistency among final recommendations. Topic editors consulted with one another when issues overlapped. For example, the decision regarding the use of a vitamin K antagonist, aspirin, and clopidogrel simultaneously in patients with atrial fibrillation, valvular disease, and intravascular stents is relevant for the atrial fibrillation, coronary, and peripheral arterial disease articles. Topic panels deferred to the Evidence-Based Management of Anticoagulant Therapy AT9 topic panel for recommendations related to the dosing and monitoring of anticoagulation therapies.

The AT9 Executive Committee met at least once a month and regularly issued statements of clarification of methods to topic editors and deputy editors (e.g., use of fixed- or random-effects models for meta-analysis), conflict of interest, preparation of tables, and issues of style and presentation. All these statements were communicated directly to the topic editors and deputy editors and made available in a central repository

accessible to all AT9 panelists. The chair of the Executive Committee was available for resolving any challenging issues related to the aforementioned topics. Between September 2009 and September 2010, two members of the Executive Committee held regular (every 3 months), separate conference calls with each topic editor and deputy editor during which they addressed questions and concerns. Finally, the chair of the Executive Committee reviewed every article to ensure consistency of evidence presentation, evaluation, and writing style. Refer to the methodology companion for further information on the approach used to ensure consistent language in writing.

Formulating Recommendations

Following approaches recommended by the GRADE Working Group, the topic editor, in some cases aided by a panelist without conflicts, formulated the draft recommendations. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled 1. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled 2. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation.

Finalizing Recommendations

The topic panel members without primary conflicts discussed draft recommendations. Initial discussions generally led to a consensus at the article level on the quality of evidence and the direction and strength of recommendations. At least two members of the Executive Committee reviewed in detail drafts of articles, including recommendations. Written critiques were prepared and returned to the authors for revision. Articles were then made available to the entire AT9 panel.

Recommendations on which topic panels had difficulty coming to a consensus were discussed at a final conference in February 2011 attended by the topic editors and deputy editors and at least one other panel member from each article. Prior to the conference, all AT9 panelists updated their conflict of interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline topic to attend the final conference as observers.

At this final conference, a representative of each article presented potentially controversial issues in their article's recommendations. Following discussion, which included those present and those attending by video conference, all panelists without primary conflicts of interest voted on each recommendation. The voting process used a GRADE grid and required that for a strong recommendation, ≥80% of those voting had to agree that a strong recommendation was appropriate.

The AT9 Executive Committee members harmonized the articles and resolved remaining disagreements among them through facilitated discussion with topic editors and deputy editors without primary conflicts. All major correspondence and decisions at the final conference were recorded in written and audio formats and are available on request to science@chestnet.org.

See the methodology companion (see the "Availability of Companion Documents" field) for information on accounting for patient values and preferences in recommendations.

# Rating Scheme for the Strength of the Recommendations

Strength of the Recommendations Grading System

| Grade of Recommendation* | Benefit vs. Risk and Burdens | Methodologic Quality of Supporting Evidence | Implications |
|---|---|---|---|
| Strong recommendation, high-quality evidence, Grade 1A | Benefits clearly outweigh risk and burdens or vice versa | Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies | Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect |
| Strong recommendation, moderate-quality evidence, Grade | Benefits clearly outweigh risk and burdens or vice versa | Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence | Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate |

| Grade of Recommendation* | Benefit vs. Risk and Burdens | Methodologic Quality of Supporting Evidence | Implications |
|---|---|---|---|
| Strong recommendation, low- or very-low-quality evidence, Grade 1C | Benefits clearly outweigh risk and burdens or vice versa | Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence | Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate |
| Weak recommendation, high-quality evidence, Grade 2A | Benefits closely balanced with risks and burden | Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies | The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect |
| Weak recommendation, moderate-quality evidence, Grade 2B | Benefits closely balanced with risks and burden | Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies | Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate |
| Weak recommendation, low- or very-low-quality evidence, Grade 2C | Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced | Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence | Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate |

*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.

## Cost Analysis

Resource Use Issues

In addressing resource use (cost) issues in Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9), the expert panel followed previously developed principles. In particular, the panel restricted economic evaluation to recommendations in which it was plausible that resource use considerations might change the direction or strength of the recommendation and in which high-quality economic evaluations were available. When this was not the case, the panel did not consider resource use in the recommendations.

Six clinicians with the requisite expertise in decision and economic analyses participated in the guideline development process; each article had the benefit of one of these experts as a full committee member. The following subsections present key points in the process of considering resource allocation issues in the recommendations.

*Overview of the Process*

Panelists, in consultation with resource use consultants, determined questions for which resource use might change the direction or strength of recommendations. For those questions, the panel sought high-quality economic analyses. If such analyses were available, the panel applied the evidence regarding resource use to the relevant recommendation. If net costs or marginal cost-effectiveness ratios were very high, panelists considered rating down the quality of evidence for an intervention from high to low or possibly changing the direction of the recommendation using guides described in the section "Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness" in the methodology companion (see the "Availability of Companion Documents" field).

*Identifying the Literature*

The Oregon Health & Science University Evidence-based Practice Center conducted thorough literature searches for economic analyses relevant to the different AT9 articles. The resource use experts supplemented these by searches focused on the specific questions of interest for each article. The searches were conducted in Medline and the Cochrane Central Register of Clinical Trials. On the basis that data from studies appreciably more than a decade old would not reflect the current situation, searches were restricted to published studies from 1999 forward. Thus, bibliographic database searches encompassed publications from January 1999 forward: The end date varied across articles and ranged between

November 2009 and March 2010 when the searches were executed.

*Evaluating the Evidence*

A standardized data extraction form was used to ensure uniform evaluation of the quality of relevant economic analyses. Quality assessment was based on published criteria and included specification of perspective of analysis (e.g., societal, health system), appropriateness of time horizon (preferably lifetime), use of high-quality evidence for probabilities and rates, use of high-quality sources for costs (e.g., primary data, Medicare payments, claims data as proxies), use of appropriate methods for measurement of preferences, and performance of sensitivity analyses to explore uncertainty (both deterministic and probabilistic).

*Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness*

The results of economic analyses may either increase the strength of an otherwise weak recommendation or weaken the strength of a strong recommendation. If cost-effectiveness studies bolstered an already strong recommendation, no change to the recommendation was necessary. The panel chose the following thresholds for cost-effectiveness considerations affecting recommendations:

1. When the clinical evidence warrants a strong recommendation for A over B:
   a. Strong recommendation favoring A when high-quality evidence from economic evaluations shows that A costs <3 times the gross domestic product (GDP) per capita (approximately US $150,000) per quality-adjusted life year (QALY) gained relative to B
   b. Weak recommendation favoring A when high-quality evidence from economic evaluations shows that A costs 3 to 5 times the GDP per capita (~$150,000-$250,000) per QALY gained relative to B
   c. Weak recommendation favoring B when high-quality evidence from economic evaluations shows that A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B
2. When the clinical evidence warrants a weak recommendation for A over B:
   a. Strong recommendation favoring A if A results in cost savings of >10% to 20% of the GDP per capita (~$5,000-$10,000) relative to B (Cost savings must represent all downstream costs and not just the actual cost of the intervention, and analysis must demonstrate a high level of confidence that there is a cost savings.)
   b. Continued weak recommendation favoring A when B is marginally more costly than A (<10% the GDP per capita)
   c. Continued weak recommendation favoring A when A costs 0 to 5 times the GDP per capita per QALY gained relative to B
   d. Weak recommendation favoring B if A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B

*Extension of Economic Analyses to Low- and Middle-Income Countries*

Although certain interventions may be cost-effective in high-income countries (e.g., <$20,000 per QALY gained), in poor countries, $20,000 gained per QALY may be prohibitive. The choice of a threshold will vary depending on who is making resource allocation decisions. To facilitate the use of already published cost-effectiveness analyses, the World Health Organization (WHO), through its WHO-CHOICE (Choosing Interventions that are Cost Effective) program has used criteria suggested by the Commission on Macroeconomics and Health. Interventions that cost <1 times the average per-capita income for a given country or region per QALY gained are considered very cost-effective. Interventions that cost up to three times the average per-capita income per QALY gained are still considered cost-effective, whereas those that exceed this level are not considered to be cost-effective. To facilitate this process, WHO has developed tables of such threshold values for different regions and countries around the world. Thus, the thresholds discussed in the previous section have been defined in terms of GDP per capita. Although referencing thresholds for cost-effectiveness to average per-capita income in middle- and low-income countries can help to extend results of economic analyses performed in high-income countries, such analyses may be less relevant in low-income countries because of significantly different material and labor costs and, thus, may be difficult to extrapolate. Furthermore, the comparator strategies may not be feasible or customary in these locales.


# Method of Guideline Validation

External Peer Review

Internal Peer Review


# Description of Method of Guideline Validation

The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed

(AT9) Executive Committee, the guidelines underwent review by the Cardiovascular and Pulmonary Vascular NetWorks of the ACCP, the HSP Committee, and the ACCP Board of Regents. The latter two groups had the right of approval or disapproval but usually worked with the topic panelists and editors to make necessary revisions prior to final approval. Both the HSP Committee and the Board of Regents identified primary reviewers who read the full set of articles, and the remaining HSP Committee members were responsible for reviewing several articles each. The reviewers considered both content and methodology as well as whether there was balanced reporting and adherence to HSP Committee processes. All reviewers were vetted through the same conflict of interest disclosure and management process described in the "Description of Methods Used to Formulate the Recommendations" field. Finally, the Editor in Chief of *CHEST* read and forwarded the manuscripts for independent, external peer review prior to acceptance for publication. No recommendations or assessments of the quality of the evidence could be changed without the express approval of the topic panel members, AT9 Executive Committee, HSP Committee, and ACCP Board of Regents.

This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate diagnosis and prevention of deep vein thrombosis (DVT)

## Potential Harms

- Venography is expensive, not uniformly available, uncomfortable for patients, and contraindicated in patients with renal insufficiency and severe allergic reactions to contrast medium. Adverse reactions to contrast media include dizziness and nausea (complicating between 1% and 4% of procedures), severe allergic reactions, and post-venography deep vein thrombosis (DVT) (confirmed by repeat venography).
- Potential adverse effects of in utero radiation exposure include oncogenicity and teratogenicity. Radiation doses of ≤5 rads do not appear to be associated with an increased risk of pregnancy loss, and it has been suggested that the risk of fetal malformation only increases above background levels at radiation doses >15 rads. However, studies have reported up to a twofold increase in the risk of childhood malignancies with radiation exposures of up to 5 rads. In absolute terms, this equates to a potential increase in the incidence of cancer in the first year of life from 0.1% to 0.2%.
- Harmful effects of a given diagnostic strategy include not only acute (e.g., renal toxicity) and long-term (e.g., cancer secondary to radiation exposure) complications but also indirect complications associated with the incorrect diagnosis (e.g., bleeding) or exclusion (subsequent DVT and/or pulmonary embolism) of DVT.
- In hospitalized and other acutely ill patients commonly affected by DVT and pulmonary embolism, D-dimer testing has less usefulness because of the high frequency of false-positive results.

# Contraindications

## Contraindications

Venography is contraindicated in patients with renal insufficiency and severe allergic reactions to contrast medium.

# Qualifying Statements

## Qualifying Statements

- The evidence-based practice guidelines published by The American College of Chest Physicians ("ACCP") incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any specific condition. Furthermore, guidelines may not be complete or accurate because new studies that have been published too late in the process of guideline development or after publication are not incorporated into any particular guideline before it is disseminated. The ACCP and its officers, regents, governors, executive committee, members and employees (the "ACCP Parties") disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied. Guideline users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline. The ACCP Parties further disclaim all liability for any damages whatsoever (including, without limitation, direct, indirect, incidental, punitive, or consequential damages) arising out of the use, inability to use, or the results of use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice of the possibility of such damages.
- Through a comprehensive and systematic literature review, the ACCP's evidence-based clinical practice guidelines incorporate data from the existing peer-reviewed literature. This literature meets the prespecified inclusion criteria for the clinical research question, which ACCP considers, at the time of publication, to be the best evidence available for general clinical information purposes. This evidence is of varying quality from original studies of varying methodological rigor. The ACCP recommends that performance measures for quality improvement, performance-based reimbursement, and public reporting purposes should be based on rigorously developed guideline recommendations. However, not all recommendations graded highly according to the ACCP grading system (1A, 1B) are necessarily appropriate for development into such performance measures, and each one should be analyzed individually for importance, feasibility, usability, and scientific acceptability (National Quality Forum criteria). Performance measures developers should exercise caution in basing measures on recommendations that are graded 1C, 2A, 2B, and 2C, according to the ACCP Grading System as these should generally not be used in performance measures for quality improvement, performance-based reimbursement, and public reporting purposes.
- Limitations of Methods: Although encouraged to use Evidence Profiles and Summary of Findings tables for all recommendations, there were some for which the authors were unable to produce such tables. However, those recommendations used an evidence-based systematic review and assessment of relevant studies. Some recommendations would have benefited from meta-analyses that would have clarified aspects of the evidence. Although panelists were instructed in completing the value and preference rating exercise to estimate patient values and preferences rather than to use their own, it cannot be assured that they succeeded in all instances.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

Clinical Algorithm

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S. [228 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Feb

## Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

## Source(s) of Funding

The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines received support from the National Heart, Lung, and Blood Institute [R13 HL104758] and Bayer Schering Pharma AG. Support in the form of educational grants were also provided by Bristol-Myers Squibb; Pfizer, Inc; Canyon Pharmaceuticals; and sanofi-aventis US.

The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations.

## Guideline Committee

American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

## Composition of Group That Authored the Guideline

*Primary Authors*: Shannon M. Bates, MDCM; Roman Jaeschke, MD; Scott M. Stevens, MD; Steve Goodacre, MBChB, PhD; Philip S. Wells, MD; Matthew D. Stevenson, PhD; Clive Kearon, MD, PhD; Holger J. Schunemann, MD, PhD, FCCP; Mark Crowther, MD; Stephen G.

Pauker, MD; Regina Makdissi, MD; and Gordon H. Guyatt, MD, FCCP

*Executive Committee*: Gordon H. Guyatt, MD, FCCP (*Chair*); Elie A. Akl, MD, MPH, PhD; Mark Crowther, MD; David D. Gutterman, MD, FCCP; Holger J. Schünemann, MD, PhD, FCCP; Sandra Zelman Lewis, PhD, ACCP; Joe Ornelas, DC

*Panelists*: Walter Ageno, MD; Pablo Alonso-Coello, MD, PhD; Sonia S. Anand, MD, PhD; Juan I. Arcelus, MD, PhD; Trevor P. Baglin, MBChB, PhD; Alex A. Balekian, MD, MSHS; Shannon M. Bates, MDCM; Sergio Bellmunt, MD; Neera Bhatnagar, MLIS; Robert Bona, MD; Henri Bounameaux, MD; Anthony K. C. Chan, MBBS; Clifford W. Colwell Jr, MD; Anthony J. Comerota, MD; Deborah J. Cook, MD, MSc(Epi); Michael H. Criqui, MD, MPH; Catherine Curley, MD; Mary Cushman, MD; Ola E. Dahl, MD; Antonio L. Dans, MD; Bruce L. Davidson, MD, MPH, FCCP; Francesco Dentali, MD; James D. Douketis, MD, FCCP; Andrew S. Dunn, MD; Shanil Ebrahim, MSc; Mark H. Eckman, MD; John W. Eikelboom, MBBS; Yngve Falck-Ytter, MD; Margaret C. Fang, MD, MPH; Jason Fish, MD, MSHS; Charles W. Francis, MD; Stephen E. Fremes, MD, FCCP; Alexander S. Gallus, MBBS; David A. Garcia, MD; Alan S. Go, MD; Neil A. Goldenberg, MD, PhD; Samuel Z. Goldhaber, MD, FCCP; Steven Goodacre, MBChB, PhD; Joel M. Gore, MD; Michael K. Gould, MD, FCCP; Ian A. Greer, MD, FCCP; Randolph Guzman, MD, RVT; Jonathan L. Halperin, MD; John A. Heit, MD; Jack Hirsh, MD, FCCP; Anne Holbrook, MD, PharmD; Patricia A. Howard, PharmD; Michael Hughes, PhD; Elaine M. Hylek, MD, MPH; Rebecca N. Ichord, MD; Roman Jaeschke, MD; Amir K. Jaffer, MD; Milosz Jankowski, MD, PhD; Norman A. Johanson, MD; Janna M. Journeycake, MD, MSCS; Susan R. Kahn, MD; Paul J. Karanicolas, MD, PhD; Clive Kearon, MD, PhD; Pooja Khatri, MD; Russell C. Klein, MD; Michael J. Kovacs, MD; Regina Kunz, MD, MSc(Epi); Deirdre A. Lane, PhD; Eddy S. Lang, MDCM; Maarten G. Lansberg, MD, PhD; Hoang Le, MD, FCCP; Wendy Lim, MD; A. Michael Lincoff, MD; Lori-Ann Linkins, MD; Gregory Y. H. Lip, MD; Samantha MacLean, MSc; Regina Makdissi, MD; Warren J. Manning, MD; Michael Mayr, MD; Marian S. McDonagh, PharmD; Shelley McLeod, MSc; Catherine McGorrian, MBBCh, BAO; Saskia Middeldorp, MD, PhD; Paul Monagle, MBBS, MD, FCCP; COL Lisa K. Moores, MC, USA, FCCP; Sohail Mulla, BHSc; M. Hassan Murad, MD, MPH; Michael E. Nelson, MD, FCCP; Mai N. Nguyen-Huynh, MD; Susan L. Norris, MD, MPH; Ulrike Nowak-Göttl, MD; Martin J. O'Donnell, MB, PhD; Thomas L. Ortel, MD, PhD; Gualtiero Palareti, MD; Stephen G. Pauker, MD; Anne-Marie Prabulos, MD; Paolo Prandoni, MD, PhD; Fraser D. Rubens, MD; Charles M. Samama, MD, PhD, FCCP; Meyer Michel Samama, MD; Sam Schulman, MD, PhD; Neil E. Schwartz, MD, PhD; Daniel E. Singer, MD; Frank A. Sonnenberg, MD; Frederick A. Spencer, MD; Alex C. Spyropoulos, MD, FCCP; Scott M. Stevens, MD; Matthew D. Stevenson, PhD; Jack Sun, MD; Peter J. Svensson, MD, PhD; Kevin H. Teoh, MD; Per Olav Vandvik, MD, PhD; David L. Veenstra, PharmD, PhD; Sara K. Vesely, PhD; Jeffrey I. Weitz, MD, FCCP; Philip S. Wells, MD; Richard P. Whitlock, MD; Daniel M. Witt, PharmD, FCCP; Ann Wittkowsky, PharmD, FCCP; Sherry M. Wren, MD; John J. You, MD

## Financial Disclosures/Conflicts of Interest

All panelists were required to disclose both financial conflicts of interest, such as receipt of funds for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious). The operational definition of primary intellectual conflicts of interest included authorship of original studies and peer-reviewed grant funding (government, not-for-profit organizations) directly bearing on a recommendation. The operational definition of primary financial conflicts of interest included consultancies, advisory board membership, and the like from industry. Topic editors had no primary conflicts of interest, as noted. Some deputy editors, who were clinical experts in the topic of the article, had relevant primary conflicts of interest. The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee deemed some of these conflicts serious enough to require "management.' Management involved more frequent updates of disclosures than required of the approved panelists without any conflicts and recusal from activities relevant to that conflict.

Topic panel members, including the deputy editor, with primary conflicts related to a particular recommendation did not participate in the final deliberations that led to the decision regarding the direction or strength of a recommendation, nor did they vote on recommendations for which they were primarily conflicted. Panelists with primary conflicts could, however, participate in discussions and offer their opinions on interpretations of the evidence. Readers will find a record of panelist conflicts of interest on a recommendation-by-recommendation basis in the online data supplement.

In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Bates has received peer-reviewed research funding for studies evaluating D-dimer in the diagnosis of deep vein thrombosis, as well as research support from Trinity Biotech and Diagnostica Stago (manufacturers of D-dimer assays). Dr Goodacre was Chief Investigator for the project "Non Invasive Diagnostic Tests for DVT," funded by the UK National Institute for Health Research Health Technology Assessment Programme, reference HTA 02/03/01, from 2003-2006 (see http://www.hta.ac.uk/1340                    ). Dr Stevenson participated in this project. Dr Kearon is a paid Steering Committee member for Boehringer Ingelheim VTE treatment studies, receives grant support from the National Institutes of Health for a study evaluating catheter-directed thrombolysis for treatment of DVT, and receives grant support from the Canadian Institutes of Health Research for a study evaluating D-dimer in the treatment of VTE. He has also received industry support for studies evaluating D-dimer, including grants and in-kind D-dimer kit

supplies. Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, has sat on Data Safety Monitoring Boards (DSMBs), and his institution has received research funds from the following companies: Leo Pharma, Pfizer, Boehringer Ingelheim, Bayer, Octapharma, CSL Behring, and Artisan. His personal total compensation for these activities over the last 3 years totals less than $10,000. Further, Dr Crowther has provided expert testimony for Bayer in an area unrelated to antithrombotic therapy. He holds the Leo Pharma Chair in Thromboembolism Research at McMaster University. Dr Wells has received peer-reviewed and investigator-initiated industry research funding for projects related to venous thrombosis treatment. He has received honoraria for industry-sponsored (Bayer, Boehringer Ingelheim, Pfizer, BioMerieux, sanofi-aventis) talks pertaining to venous thrombosis and has attended advisory boards for Bayer, Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb. Drs Guyatt and Schunemann are co-chairs of the GRADE Working Group, and Dr Jaeschke is a prominent contributor to the GRADE Working Group. Drs Stevens, Pauker, and Makdissi have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org _____.

# Guideline Endorser(s)

American Association for Clinical Chemistry, Inc. - Professional Association

American College of Clinical Pharmacy - Medical Specialty Society

American Society of Health-System Pharmacists - Professional Association

American Society of Hematology - Medical Specialty Society

International Society on Thrombosis and Haemostasis - Professional Association

# Guideline Status

This is the current release of the guideline.

# Guideline Availability

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal _____.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

# Availability of Companion Documents

The following are available:

- Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;7S-47S.
- Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical guidelines. Chest 2012;141;48S-52S.
- Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;53S-70S.
- Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e1S-e23S.
- Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e44S-e88S.
- Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based

clinical practice guidelines. Chest 2012;141;e89S-e119S.

- New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e120S-e151S.
- Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e185S-e194S.

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal _____.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on May 2, 2012.

## Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

# Disclaimer

## NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.